AMICROBIC PYURIA*

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IN the last decade treatment of infections of the urinary tract has been fairly well standardized. Certain general principles of diagnosis and treatment have been laid down and are well known. To me, the most interesting part of the whole problem of urinary infections is its relative simplicity, for if the general physician and the urologist will approach the question of treatment with a few well-organized principles in mind, a large percentage of infections of the urinary tract may be cleared up early and completely before they have time to produce changes in the kidneys, ureters or bladder which materially complicate the problem.

It seems unnecessary to mention to a group of urologists that first of all, before treatment is undertaken, the presence of an infection of the urinary tract and the general site of the infection should be established. Each year my colleagues and I at the Mayo Clinic see a number of women patients who have been taking mandelic acid or one of the sulfonamides to the point of tolerance in an effort to eradicate an infection of the bladder and kidneys which actually does not exist. It is true that these patients have burning and frequent urination and pus in the urine. The administration of various chemotherapeutic agents, however, has produced little if any benefit. On questioning the patient it often is found that only voided specimens of urine were examined, and when a catheterized specimen is examined, it is entirely free of pus or organisms. In this group of cases the detailed examination and history suggest inflammation of the urethra, and cystoscopy frequently reveals chronic granular or cicatricial urethritis or both. Local treatment for a few days is usually of great benefit and the patient is relieved.

In men pyuria frequently can be proved to be of prostatic origin. Chemotherapy for this type of pyuria is of little value. Thus, when females have pyuria or other symptoms of urinary infection a specimen

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of catheterized urine must be examined and when males have these symptoms the two-glass test of urine should be done routinely before treatment is instituted in order to determine whether the infection may involve the kidneys, ureters, or bladder.

Having once established the presence of an infection of the kidneys, ureters or bladder, it is now of value to determine the type of organism producing the disease and the presence or absence of any primary or secondary contributing pathologic infection. By no means do I wish to infer that every patient suffering from an infection of the urinary tract should have a complete urologic examination, including urographic and cystoscopic studies. However, I do feel that because of the well-known efficacy of mandelic acid and the sulfonamides in eradicating uncomplicated infections of the kidneys, ureters and bladder the use of these drugs should not be continued indefinitely. If two courses of treatment do not bring about sterilization of the urine, then the patient is entitled to a complete urologic examination in order to ascertain the presence of any existing condition in the urinary tract, such as stone, stasis, tumor, and so forth, which is hindering the action of the drug.

The importance of the infecting organism has been clearly demonstrated, but a few words of repetition seem indicated. Simple Gram's staining of the urinary sediment should be done in every suspected case. Examination of slides after Gram's staining will divide the cases into two groups: the first, those with demonstrable organisms, and the second, those without demonstrable organisms. It will divide the first group further and indicate to the physician whether he is dealing with a bacillary or coccal infection and whether the organism is gram-positive or gram-negative.

It is the second and smaller group of cases without demonstrable organisms which I should like to discuss in detail in this paper, because I am certain that their existence is not fully appreciated by either the general physician or the urologist. All physicians were taught early in their training to consider sterile or amicrobic pyuria indicative of a tuberculous infection of the urinary tract. Undoubtedly, this is the usual cause but by no means does it account for all such cases. What then is the etiologic factor in these cases?[1-4] Is an ultramicroscopic organism or a filtrable virus the causative agent? Is bacterial invasion of the renal parenchyma present without any organism reaching the tubules and hence the urine? If such invasion occurs, are the cellular elements

in the urine the result of the inflammation produced by the liberated toxin? Another possibility is that the toxins liberated by foci of infection elsewhere in the body are excreted by the kidneys and produce the resulting inflammatory reaction. Ewert and Hoffman,[5] Moore,[6] and others in their writings suggest an ultramicroscopic organism or filtrable virus as the most likely cause of pyuria without demonstrable organisms. Studies at the Mayo Clinic certainly cannot disprove this hypothesis but I feel that in a large number of cases foci of infection elsewhere in the body contribute to the etiology of the inflammatory reaction in the urinary tract, and unless these foci are eradicated, complete cure is difficult to obtain.

The duration of the disease varies. Originally it was my impression that it was present for months or even years in most cases but as ability to recognize it increased a number of patients have been seen early in their illness. The local symptoms are referred to the bladder and urethra and are usually severe—more severe, indeed, than those seen in the usual bacillary or coccal infections of the urinary tract. Dysuria and frequent urination with tenesmus are the rule. Sometimes there is hematuria and on occasions the distress reaches the point of stranguria. Systemic reactions are not common but in a few cases pain in the loin with chills and fever, general malaise, anorexia, and so forth have been noted.

The urine is loaded with cellular elements; leukocytes, erythrocytes and epithelial debris. Repeated Gram's staining and staining of the urinary sediment for acid-fast bacilli and repeated cultural studies fail to reveal any infecting organisms. The finding of so-called sterile pyuria, of course, should bring to the examiner's mind the possibility of a tuberculous infection and this condition must be ruled out by repeated use of stains to indicate acid-fast bacilli and inoculations of guinea-pigs. A large number of the patients suffering from such pyuria not due to tuberculosis have been submitted to an intensive anti-tuberculosis regimen which entailed an entirely unnecessary economic burden. Because of the occasional difficulty in finding the tuberculous organisms in stained slides of urine and the length of time required to carry out the guinea-pig test, a tentative diagnosis of tuberculosis is made. However, failure to find certain clinical signs of tuberculosis of the urinary tract should tend to exclude this condition even before the laboratory reports are received. These signs, however, generally are not known. Bumpus and Thompson[3] have shown that in 80 per cent of

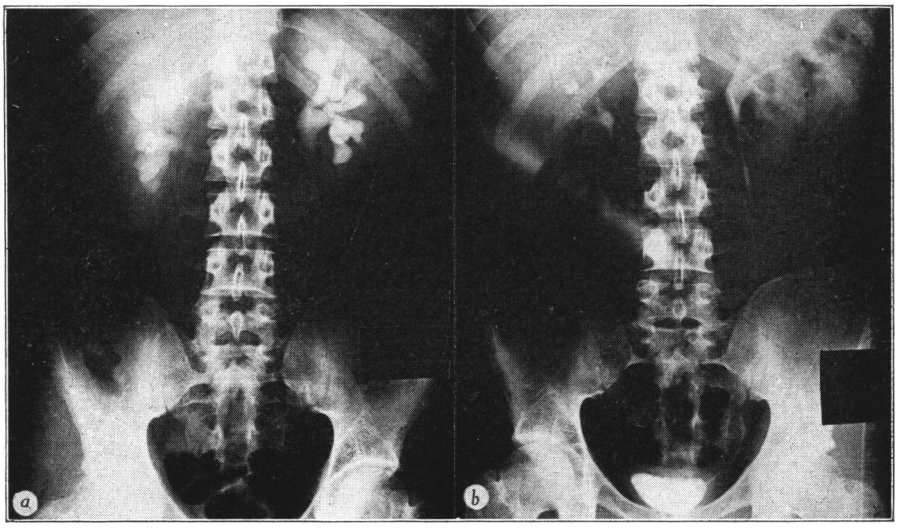

Fig. 1—Urograms in a case of amicrobic pyuria *a*, before treatment; dilatation of the renal pelvis and calices may be noted; *b*, after treatment.

the cases of tuberculosis of the upper part of the urinary tract the genitalia are involved also. In such cases the clinical findings are nodular and thickened epididymides, beaded pipestem vasa deferentia, or nodular prostate gland. The diagnosis of tuberculosis should never be made without corroborative evidence other than the apparently sterile pyuria and some suggestive cystoscopic or urographic findings.

Cystoscopic findings in cases in which non-tuberculous, sterile pyuria is present are a reduced vesical capacity, extreme irritability and diffuse involvement of the vesical mucosa with redness, edema and at times ulceration. These findings usually appear to be superficial, but in the cases of infection of long standing the deeper tissues seem involved as well. Ureteral catheterization almost always reveals bilateral renal infection of varying degree. One side may be involved to a greater degree than the other side. Renal function is rarely impaired except in the late stage of the disease.

Urography frequently discloses dilatation of the pelves, calices and ureters which is suggestive of an inflammatory origin, and in other cases the urographic findings are negative. Positive urographic findings may invite a certain pessimism with regard to prognosis but this should not be. Urograms made in the case of a young man (Fig. 1*a* and *b*) suffering from this type of infection of the urinary tract indicate the

change in conditions before and after treatment. The return to normal is frequently noticed if the disease is not too longstanding.

Experience during the last decade has taught a great deal regarding treatment of these conditions. Primarily it has been learned that the usual urinary antiseptics given by mouth are of little or no value. None of the sulfonamide compounds or mandelic acid is effective in relieving symptoms or reducing the pyuria. Local therapy if carried out intensively may be helpful but by no means is it as useful as in the infections with demonstrable organisms. In a few cases the infection is so severe that examination is required in the hospital, and continuous irrigating systems for vesical lavage must be employed. In these cases gradually increasing strengths of solutions of silver nitrate, beginning with a 1:10,000 solution and proceeding to a 1:1,000 solution, if possible, have been used with benefit. This type of lavage, however, is usually only a palliative measure. Most observers agree that the therapeutic weapon of choice in combating this disease is the intravenous use of an arsenical preparation. Improvement usually comes after the first or second injection in our experience.[2] This experience has been confirmed recently by Ewert and Hoffman.[3] Occasionally a third or fourth injection may be required but this is not the rule. In my experience small doses of neoarsphenamine are just as efficacious as the larger doses, and I recommend 0.2 gm. for the first dose, followed in four to five days by a dose of 0.3 gm., with subsequent doses, if needed, given at the same interval and of the same size. Because of the excellent results which usually follow the administration of the arsenicals intravenously, it has been supposed that a spirochete might be the etiologic agent. However, Wildbolz[7] has called attention to the fact that the Wassermann reaction on the blood for syphilis and examination of the urine for the presence of spirochetes by dark-field illumination always give negative results.

Having discussed the most important therapeutic procedure, I wish now to say a few words concerning what I believe to be a definite adjunct to treatment and in some cases a positive requirement. I always hesitate to suggest foci of infection as the reason for a urologic disorder. This hesitancy exists because of the difficulty of proof and also because I do not wish to encourage the indiscriminate removal of teeth or tonsils for infections of the urinary tract. However, in a large group of these cases in which initial improvement has been brought

about by the administration of the arsenicals, removal of any foci has produced a definite exacerbation of the symptoms with an increase in the urinary findings. This observation certainly seems to suggest a relationship. Furthermore, in a few patients who have recurrent trouble even after taking arsenicals, removal of foci has brought about a complete cure. Foci are important and should be borne in mind. The teeth and tonsils should be investigated carefully; the prostate gland should be examined and massaged if infection is found, or the cervix uteri should be carefully checked and treatment instituted if necessary.

Report of Case

A white man, twenty-one years of age, registered at the clinic November 1, 1943. His main complaint was burning and frequent urination, hematuria, and extreme dysuria of four months' duration. Examination at home had revealed a bladder of small capacity, severe cystitis and definite reduction of renal function as shown by the excretory urogram. Early hydronephrosis was noted on both sides. Staining of the urinary sediment was reported to show acid-fast bacilli. Inoculations of guinea-pigs had not been made.

At the time of examination at the clinic the patient was wearing a urinal because of the extreme frequency and urgency. His tonsils were grossly infected and exuding pus. There was definite suprapubic tenderness and his prostate gland was tender on rectal examination. The genitalia were otherwise normal. The significant laboratory data revealed pus, grade 4, and erythrocytes, grade 4, in the urinary sediment but all the staining and cultures of the urine failed to reveal the usual invading organisms as well as the acid-fast organisms of tuberculosis. Visualization of both kidneys was delayed in the excretory urogram and there was dilatation of the pelvis, calices and ureters, grade 2. Cystoscopic examinations under pentothal sodium anesthesia revealed acute diffuse cystitis, grade 4, which was not suggestive of tuberculosis.

Continuous vesical lavage with 1:10,000 of silver nitrate was begun and continued for one week. The patient then was dismissed from the hospital and local treatment as described previously was carried out in the office twice daily. He was given one injection of neoarsphenamine and this medication brought about real improvement in his condition. Five days later a second injection was given with further improvement but unfortunately toxic erythema developed and further treatment of

this nature was impossible. His situation remained about the same for another week and tonsillectomy was advised. This was done and was followed by a definite exacerbation of all his vesical symptoms for two or three days. Local treatment was continued and in one week following tonsillectomy all symptoms had disappeared. The urine continued to show pyuria, grade 3, but with lavage and prostatic massage, the urine cleared up and the patient was dismissed as cured. An excretory urogram just before dismissal was entirely negative and cystoscopic examination gave negative results except for a few patches of redness over the trigone of the bladder.

Comment

The main concern of this paper is a condition which is becoming better known as time goes on. However, the frequency with which it is missed seems ample justification for considering it in detail. Careful studies of the urinary sediment and cultures of the urine, when possible, are of utmost value and should be carried out in all cases. The differential diagnosis between amicrobic pyuria and tuberculosis must be made with care. This latter condition presents many problems in its diagnosis and should ever be present in the mind of the examining physician.

In the treatment of amicrobic pyuria, the usual chemotherapeutic compounds that are so efficacious in combating the ordinary infections of the urinary tract are of little value. Local treatment gives only palliation, but the intravenous administration of arsenical compounds is almost specific. Along with this, however, I should like to make a plea for the appreciation of the part which foci of infection play in many of these cases. Permanent cure will frequently be impossible unless existing foci are eradicated and the teeth, tonsils, prostate gland, and uterine cervix are the most common.

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